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Clinicopathological Characteristics in Male Breast Cancer: A Case Series and Literature Review

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Abstract

Male breast cancer (MBC) is a rare entity with overall cases reported were less than 1%. However, the incidence of MBC is regularly rising every year. Due to the lack of data on MBC, diagnosis and treatment are tailored to female breast cancer. MBC risk increases with age and is usually diagnosed ten years late as the disease progression is slow compared to female breast cancer (FBC). The most common feature of MBC is an intra-ductal variant, and often, upon diagnosis, the stage of the disease is already advanced. The Prognosis of MBC is often flawed, but new treatment modalities are emerging with the current knowledge and advancement. We presented a series of male breast cancer in our center, highlighting the clinicopathological, radiological and treatment options.

Keywords: Male Breast Cancer (MBC), Clinicopathological Feature, Ultrasonography, CT Scan

Introduction

Breast tissue is underdeveloped in males compared to females. In an adult male, the breast tissue is usually composed of fat tissues, ducts and no lobules [1]. It has been reported that after puberty there is about 10% of male adults have persistent breast tissues [2]. Early detection of MBC is difficult as the disease usually presents late in the lifetime. In a population-based study done by Anderson et al., the mean age of MBC diagnosis was 65.8 years old [3,4]. Due to its rarity and lack of data, it is not easy to understand the character and behavior of MBC. Hitherto, we are referring to female breast cancer guidelines in navigating MBC management. The risk for MBC increases with advancing age, and the prognosis is worse than female breast cancer based on overall survival [5,6]. MBC is closely related to BRCA2 mutation with 6.3% of lifetime absolute risk for breast cancer [7]. Several studies have shown that most MBC are of a ductal variant with ER-positive and Luminal type a [8]. We want to report the clinicopathological characteristics of five male breast cancer cases that we encountered in our center retrospectively.

Case A

A 72-year-old gentleman presented with the right breast swelling and painless nipple bloody discharge three months before presentation. The swelling was progressively increasing in size, with changes noted on the surface of the nipple skin. He had constitutional symptoms such as loss of weight and appetite for the past year. He lost about 10kg in six months. There was no family history of breast cancer or consuming any hormonal pills or supplements. Physical examination revealed a hard, non-tender lump at the retro areolar region measuring about (2 x 1) cm, associated with bloody serous discharge from the nipple. No mass was palpable on the other region of the breast or contralateral side. Bilateral axillary lymph nodes were not palpable. Breast

ultrasound showed a mass with mixed cystic and solid components at the retro areolar region measuring (1 x 1 x 1.8) cm. There was increased internal vascularity with a layer of sediment within the complex cystic mass (figure 1). The imaging findings were categorized as BIRADS 4. Computed tomography (CT) scan noted a focal enhancing lesion at the retro areolar region on the right breast measuring (0.8 x 0.8 x 1.0) cm with no extension to the underlying pectoralis muscle (figure 2). An ultrasound-guided biopsy was performed and confirmed intra-ductal papillary carcinoma/papillary DCIS (figure 12A). The patient was staged as T1N0M1 according to the TNM classification. The patient underwent a right mastectomy. He was then discharged home well after a week, and a surveillance mammogram was performed a year later showed no focal lesion seen on the contralateral breast.

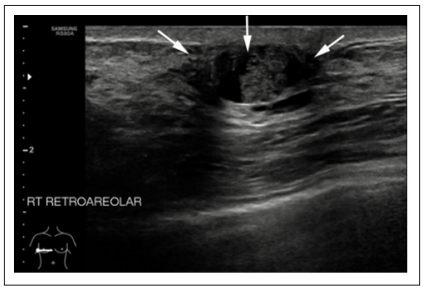

Figure 1: Ultrasound of the Right Breast Showing a Mixed Solid Cystic Lesion with Microlobulated Border at the Retro-Areolar Region

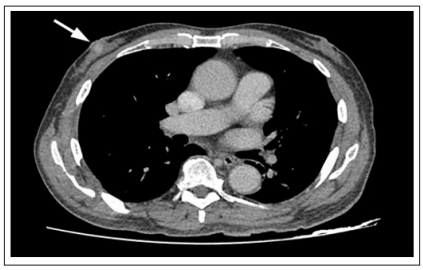

Figure 2: Axial CT Scan Thorax Showing a Focal Enhancing Lesion at the Right Retro-Areolar region. The Underlying Pectoralis Major Muscle is Preserved

Case B

A 59-year-old gentleman, an ex-chronic smoker, was referred to our center for a large left breast mass. The left breast swelling had been there for one year before the presentation. While in the ward, he developed a generalized tonic-clonic seizure (GTC) for six episodes, aborted by intravenous Phenytoin. CT brain showed a left frontal intra-axial mass suggestive of metastasis (figure 3). Clinically, the left breast swelling was irregular in shape, measuring about (18 x 5) cm, hard, non-tender and fixed to the underlying structures. The left axillary lymph nodes were palpable and mobile as well. A TRU-CUT biopsy of the left breast mass was performed, and histopathology examination was reported as invasive breast carcinoma of non-special type (NST), Modified Bloom Richardson grade 3 (figure 12B). The contrast-enhanced CT for the staging purpose showed a lobulated heterogeneously enhanced mass occupying the whole left breast measuring (11.1 x 4.7 x 9.2) cm with an erosion of the left anterior end of second to fourth lateral surfaces of the ribs and extension to the thoracic cavity (figure 4). There were multiple enhancing axillary lymph nodes bilaterally, at the pre-tracheal, para-tracheal, sub-carina and lung nodule presence in the superior segment. A metastatic lesion was seen on the left adrenal gland measuring (3.7 x 2.9 x 3.5) cm as well. The patient was staged as T4N1M1. Unfortunately, the patient deteriorated and succumbed to death due to a pulmonary embolism on day eleventh of admission.

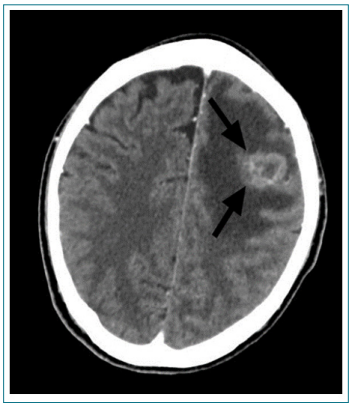

Figure 3: Contrast-Enhanced CT Scan of the Brain Showing an Intra-Axial Lesion with Thick Nodular Ring Enhancement Pattern at the Grey-White Matter Junction of the Left Frontal Region (Black Arrow). it is Associated with Extensive White Matter Edema

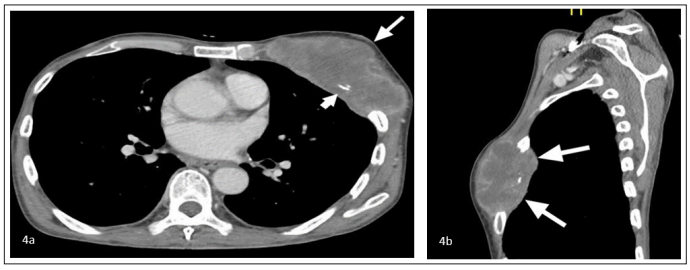

Figure 4: CT Scan Thorax (4a) Showing a Huge Mass with Necrotic Center Occupying the Whole Left Breast (White Arrow) with Infiltration to the Chest Wall, Erosion of the Adjacent Ribs (Short Arrow) and Extension of the Lesion (4b) into the Thoracic Cavity

Case C

A 74-year-old gentleman with underlying hypertension and dyslipidemia presented to our center with right breast swelling two years before the presentation. The swelling had progressively increased in size, associated with bloody nipple discharge and foul smell. Clinically, a (4 x 4) cm fungating mass at the right nipple-areolar complex (NAC) was hard, non-tender and fixed to the underlying structures. The lesion demonstrated contact bleeding during manipulation. Mobile right axillary lymph nodes were palpable. The ultrasound showed a large lobulated mass with internal calcification (figure 5). A wedge biopsy was performed, and the result revealed invasive breast carcinoma of NST. A CT scan of the thorax, abdomen, and pelvis for staging showed right breast mass with suspicious extension to the underlying pectoralis major muscle evidenced by loss of fat plane between the lesion and the muscle (figure 6). There were enlarged axillary nodes and bilateral lung nodules, which suggestive of metastasis (T4CN1M1). A right mastectomy with axillary dissection was performed, a total of 15 axillary lymph nodes were removed and sent for histological examination. The specimen's microscopic examination displayed an invasive carcinoma, NST, with evidence of epidermal infiltration consistent with stage T4B (figure 12C). There were five out of seven lymph nodes positive for tumor infiltration.

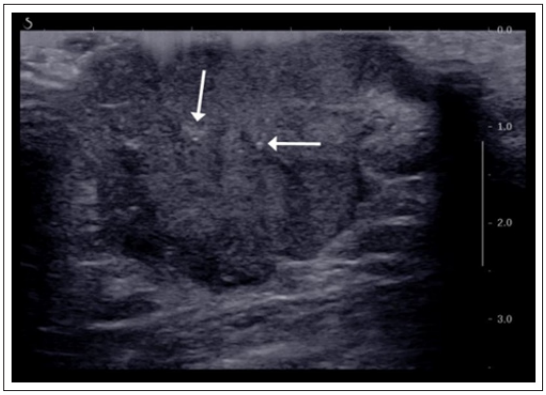

Figure 5: Ultrasound Showing a Hypoechoic Mass with Lobulated Margin at the Right Retro-Areolar Region. Presence of Multiple Punctate Calcifications within the Lesion (White Arrows)

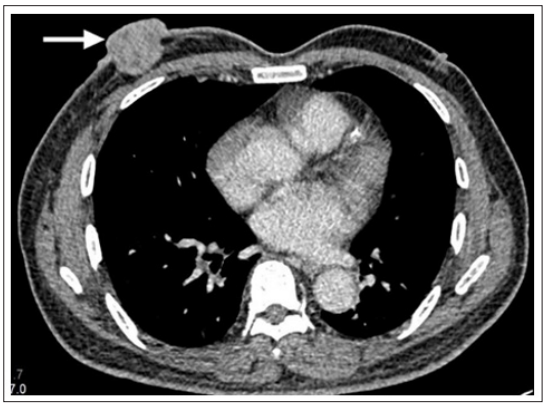

Figure 6: Axial CT Scan Thorax Showing a Lobulated Enhancing Soft Tissue Mass (Arrow) in the Right Breast, which has a Poor Fat Plane with the Pectoralis Muscle

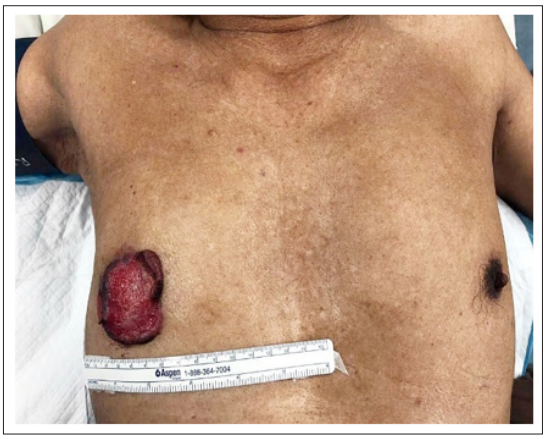

Figure 7: Pre-Operative Picture Showing Right Breast Lesion

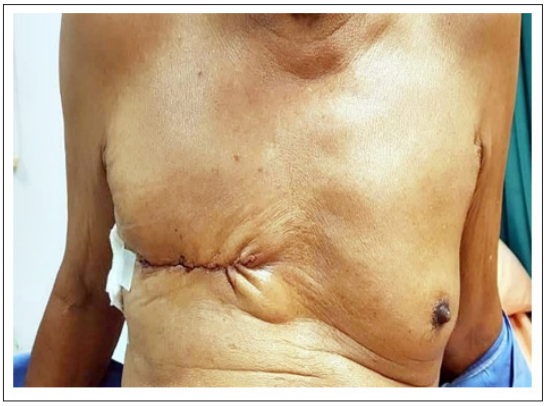

Figure 8: Post Right Mastectomy and Axillary Clearance

Case D

A 64-year-old gentleman with an underlying Stanford Type B dissecting aneurysm post endovascular aortic repair (EVAR) was referred to our breast clinic for a right breast lump. The lump has been there for three months, gradually growing more prominent. The right breast lump was associated with pain, and he was dependent on regular analgesics. The patient denies any history of trauma, nipple discharge or lump on the contralateral breast. There was no positive family history of breast cancer. There was a round swelling at the nine o'clock position upon clinical examination, 1 cm away from the right nipple, measuring (3 x 3) cm in size. The mass was firm, mobile, and non-tender. No nipple discharge or peau d'orange skin changes seen. Breast ultrasound showed a mass with microlobulated margin measures (1.9 x 3.2 x 2.7) cm at 9 o'clock, 2 cm from the nipple, heterogeneous hypoechoic in echogenicity and associated with posterior enhancement (figure 9). The mass has internal vascularity with a resistive index of 0.81. The lesion was labelled as BIRADS 4. An ultrasound-guided biopsy was performed, and the histopathology revealed an invasive breast carcinoma of no special type (NST) (figure 12D). The CT scan reported evidence of local infiltration but no distant metastasis ($T_4N_0M_0$) (figure 10). The patient was offered a mastectomy, but unfortunately, he defaulted our follow-up.

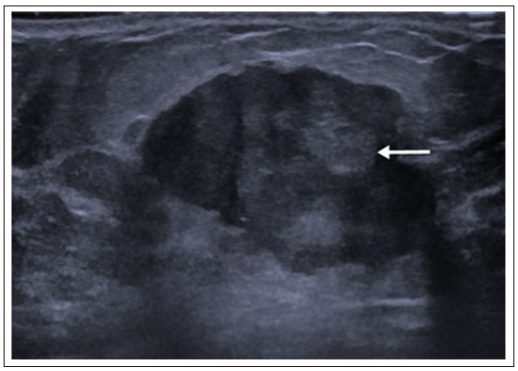

Figure 9: Ultrasound Showing a Well-Defined Lobulated Heterogeneous Hypoechoic Mass in the Right Breast. The Focus of Calcification Seen at the Hyperechoic Region Within the Lesion (White Arrow)

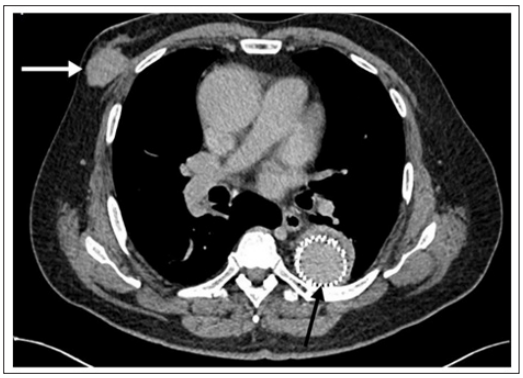

Figure 10: Axial CT Scan Thorax Showing a Homogeneously Enhancing Mass at the Right Breast (White Arrow) with Infiltration into the Underlying Right Pectoralis Major Muscle. There is Also Dilated Descending Aorta with Endovascular Graft in Situ (Black Arrow)

CASE E

A 67-year-old male with a previous history of right nipple discharge and underwent right microdochectomy 8 years before the current presentation presented with a right breast lump. He noticed the lump three months before his presentation to the hospital. The lump did not grow; otherwise, he experiences some occasional pain. There was no bloody nipple discharge, erythema,

or contralateral breast lumps. Right breast ultrasound demonstrated a well-defined rounded, anechoic lesion with posterior enhancement at 9 o'clock, peri-areolar region measuring (1.1 x 1.4 x 1.4) cm in size. There were thick internal septations with an irregular solid component within the cyst (figure 11). TNM staging for the patient was T1BN0M0. The patient underwent right mastectomy and sentinel lymph node dissection. The sentinel lymph node was identified using a combination of Technetium-99 tag and methylene blue dye. The dissected sentinel lymph node was sent for the frozen section and was negative for malignancy; thus, no axillary clearance was done. The HPE from the TRU-CUT biopsy suggestive of intraductal papillary carcinoma (DCIS). However, the interpretation was made with caution in view that no stroma was included. The mastectomy specimen harbored in situ lesions and showed an area of invasive carcinoma of NST with encapsulated papillary carcinoma (figure 12E). Histopathology report revealed that all resected margins were free from the tumor and no evidence of metastasis in the axillary lymph node. The patient was started on Tamoxifen and planned for surveillance CT thorax, abdomen, and pelvis.

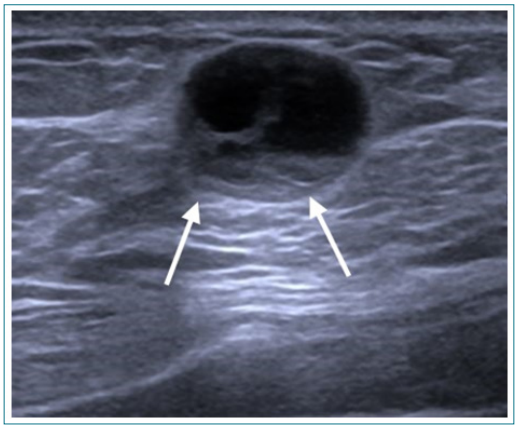

Figure 11: Ultrasound Image Showing a Well-Defined Rounded, Anechoic Lesion with Posterior Enhancement at the Right Breast. Presence of Thick Septa and Solid Component (White Arrows) within the Cyst.

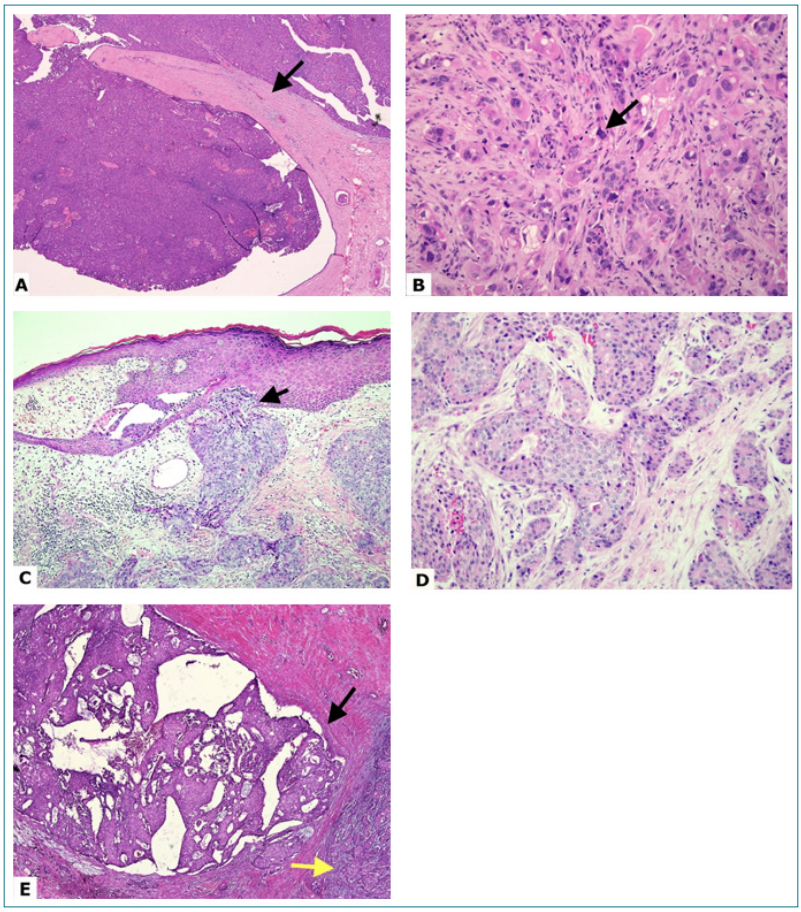

Figure 12
A (Case A): Fibrovascular Core (Black Arrow) in Intraductal Carcinoma in Situ Lined by Monotonous Proliferation of Ductal Epithelium (40X)

B (Case B): The Invasive Breast Carcinoma, NST Exhibits Marked Nuclear Pleomorphism (Black Arrow) as Compared with Mild to Moderate Nuclear Pleomorphism in Case D (200X)
C (Case C): The Tumor Cells are Arranged in Nests and Infiltrated into the Epidermis Layer (Black Arrow) (100X)
D (Case D): The Tumor Cells Exhibit Mild to Moderate Nuclear Atypia (200X)
E (Case E): Invasive Carcinoma NST (Yellow Arrow) with Adjacent Encapsulated Papillary Carcinoma (Black Arrow) (40X)

Table 1: Summary of Clinicopathological Features of Male Breast Cancer

	Case A	Case B	Case C	Case D	Case E
Age (year)	72	59	74	64	67
HPE diagnosis	Intra-ductal Papillary carcinoma (papillary DCIS)	Invasive carcinoma of no special type (NST)	Invasive carcinoma of no special type (NST)	Invasive carcinoma of no special type (NST)	Invasive carcinoma of no special type (NST) with encapsulated papillary carcinoma
Multifocality	No	No	No	No	No
Bilaterality	No	No	No	No	No
Laterality	Right	Left	Right	Right	Right
Type of surgical procedure	Mastectomy	No surgery done	Mastectomy	No surgery done	Mastectomy and sentinel lymph node dissection
Axillary lymph node dissection	No	No	Yes	No	Yes
No of positive lymph nodes	Nil	Nil	5 out of 7	Nil	Nil
Stage	$T_1N_0M_1$	$T4N_1M_1$	$T_4CN_1M_1$	$T_4N_0M_0$	$T_1BN_0M_0$
Tumor grade	Grade 2	Grade 3	Grade 3	Grade 1	Grade 2
Lymphovascular invasion	No	No	Yes	No	No
Hormonal receptor status	ER: positive PR: positive E-cadherin: positive	ER: negative PR: negative	ER: positive PR: positive	ER: positive PR: positive	ER: positive PR: positive
Her-2 status	Negative	Negative	Positive	Positive	Negative

Discussion

Male breast cancer (MBC) is a rare type of neoplasm with less than 1%overall cases. However, an annual increment of MBC has been reported in the United Kingdom, the United States and Europe [8]. There were no large-scale multicenter studies conducted in South East Asia for MBC, probably due to its rarity in this region; thus, we lack the necessary data. MBC pathology closely resembles female breast cancer (FBC). MBC is diagnosed later in the male than females, and the prognosis upon diagnosis is usually poor. The mean age of MBC in our case series is 67.2 years old. Several risk factors are related to the MBC, such as high estrogen level, radiation exposure, strong family history of breast cancer and, a rare genetic disorder such as Klinefelter's syndrome. Undescended testis, orchidectomy, orchitis and late puberty have been related to MBC [9]. In our case series, four of the patients were diagnosed with invasive breast carcinoma of no special type (NST) and one case as papillary DCIS. All patients have no multifocal nor bilateral disease. Unfortunately, four out of the five patient described presented to our center at the late stage of the disease, some with distant metastasis. Another important clinicopathological aspect that we looked upon was the tumor grade. There are several techniques for determining tumor grade. Frequently used are Bloom-Richardson grading system, which considers the gland, nuclear features, and mitotic activities. Humphries et al. reported that MBC usually exhibits grade 2 [10]. Meanwhile, two of our MBC cases are grade 3, and one case is grade 1. One patient had a mastectomy, while another two patients had a mastectomy and axillary dissection. Patient B was not operated on as he succumbed due to a pulmonary embolism (PE). One of the patients (patient D) defaulted his follow-up after clinical staging and was not contactable. Only patient C has evidence of lymphovascular invasion out of five patients. CT scan of patient C demonstrated that he had bilateral lung metastasis. Patient B was detected to have brain metastasis despite having no evidence of lymphovascular invasion. The brain metastasis in patient B was diagnosed in less than six months of breast cancer diagnosis, thus labelled as a synchronous tumor. Synchronous tumor in a breast cancer patient has been reported in several cases reports [11]. Most of our MBC patients demonstrated positives for both Estrogen and Progesterone receptors except for patient B. This correlates with most studies where MBC has a high ER/PR positivity of up to 90% [12,13]. The expression of human epidermal growth factor receptor 2 (HER-2) in MBC is rare. Only patients C and D showed positive (HER-2) while the rest were negative. Both patients (C and D) were at the T4 stage and ER/PR positive. Patient C underwent surgery and adjuvant therapy while patient D defaulted follow-up. Targeted therapy using monoclonal antibodies such as Herceptin has shown a promising result in HER-2 positive MBC patients [14]. Patient B is the only patient with triple-negative receptor status in our case series. In triple-negative breast cancer (TNBC), the cancer cells do not demonstrate estrogen or progesterone receptors nor produce enough HER-2 proteins. Treating a TNBC could be a great challenge, especially in male breast cancer with minimal data available. New studies have emerged on Novel-ADC (antibodies drug conjugate) in treating TNBC, which can be applied on aggressive MBC with triple-negative [15]. In comparison to FBC, genomic and epigenomic levels of MBC are not well studied, and only a few array-based studies have been performed investigating DNA copy number aberrations, gene expression profiles and microRNA profiles [16].MBC molecular characterization provides insights into future methods for therapy. There are various other molecular markers beyond the clinically significant receptor subtypes that have been tested in the setting of MBC. For example, microRNAs (miRNAs) represent~22 non-coding nucleotide RNAs that can modulate mRNAs' function [17].

Conclusion

Male breast cancer (MBC) is just as fatal as female breast cancer (FBC). The scarcity of cases, lack of data and the long period of disease progression making it complicated for the clinicians to manage. In our case series, most male breast cancer cases appeared at the late stage of life with an advanced tumor grade, often with distant metastasis and poor prognosis. What is promising, the majority of these patients demonstrated Estrogen and Progesterone receptor positivity which may respond to hormonal treatment

with an acceptable outcome. Other techniques for studying the disease using immunohistochemically and tumor genetics should be explored. More extensive multicenter local and international collaborations are needed in gathering more data and information about MBC. Local health facilities and the governing bodies should play a vital role in increasing the awareness of male breast cancer and conducting a screening programme in the community as MBC is a treatable and preventable disease.

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